Strong Hydrogen Bonding in Organic Synthesis

by

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Abstract

The preparation of phenacyl and para-phenylphenacyl esters, the reactions of carboxylic acids, phenols, 2-nitropropane and alcohols with alkyl halides in the presence of fluoride anion are described. The reactions are thought to be accelerated by the formation of hydrogen bonds between the fluoride anion and the organic electron acceptor. The fluoride -carboxylic acids, fluoride -phenols and fluoride-2-nitropropane are better reaction systems than the fluoride-alcohol. The source of the fluoride anion and the choice of solvents are also discussed.

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Chapter I

Introduction

In organic synthesis, alkali metal fluorides and quaternary ammonium fluorides are useful reagents. They have been used, in the past twenty years, as fluorinating agents and as sources of the fluoride ion which acts as a base. Also, quaternary ammonium fluorides can be used as phase transfer catalysts. In a review of these compounds in organic synthesis, Dockx suggested that quaternary ammonium fluorides should be the best catalysts, according to the hard and soft base principle.[1]

Use of alkali metal fluorides as fluorinating agents

The introduction of fluorine atoms into an organic molecule causes some changes in both the chemical and physical properties of the compound. Many organic fluorine compounds are useful in organic synthesis. For example, a number of fluorinated olefins, such as $CF_2=CF_2$, $CF_2=CFCl$, and $CF_2=CH_2$, react readily with alcohols, amines, mercaptans, and with themselves to give other compounds containing functional groups such as ethers, amides, etc.[2]

$$CF_2=CF_2 + NH_2R \xrightarrow{H_2O} CHF_2CONHR$$

$$CF_2=CFCl + ROH \longrightarrow CHFClCF_2OR \xrightarrow{H_2SO_4} CHFClCO_2R$$

Some organic fluorine compounds have toxic properties and cause changes in biological action in living systems. These properties were studied extensively during the years of World War II. Some organofluorine

compounds have been used in drugs and pesticides.[2,3] A number of fluorocarbon polymers, such as the polymers of tetrafluoro- and chlorotrifluoroethylene, can be used as plastics. These fluoroplastics can be used as coatings for magnetic wire, insulation for coaxial cable, and supports for radar and FM anntennae due to their excellent electric properties.[2,3] As a result, many chemists devoted a lot of effort to this field, and it became an important branch of organic chemistry.

Organic fluorine compounds can be prepared by many methods. Fluorination by halogen exchange is the most widely used one. A large number of inorganic fluorides have been studied as agents for this purpose. Alkali metal fluorides are the most common and important ones. Numerous syntheses of organic fluorine compounds, such as fluoroalkanes, fluoroalkenes, fluoroaromatics, etc., have been reported in the literature using potassium fluoride as a fluorinating agent in non-polar or polar media.[2,3]

The basic character of fluoride ion

In 1948, the basic behaviour of fluoride ion was recognized for the first time. During the reaction of trichloroacetic acid and potassium fluoride, Nesmeyanov observed a gas evolved and afterward, only chloroform was isolated instead of the expected trifluoroacetic acid.[4] He concluded that fluoride ion has basic properties in this reaction.[4] For some time after this, no further studies were carried out to investigate these particular basic properties and the possibility of their use in organic reactions.

In organic chemistry, many reactions must take place, or are more efficient, in the presence of a base. Aldol condensations, Perkin condens-

ations, Knoevenagel condensations and Michael additions are examples of this type of reaction. The first deliberate use of the fluoride ion as a base in organic synthesis was in the Knoevenagel type condensation. In 1958, M. Midorikawa and his collaborators condensed aldehydes with active methylene compounds, such as ethyl cyanoacetate and diethyl malonate, in the presence of potassium fluoride.[5] Later, they extended their work to ketones.[6] Equimolar amounts of aldehyde or ketone, ethyl cyanoacetate or diethyl malonate, and potassium fluoride were mixed in alcohol at reflux temperature for several hours giving condensation products.

$$C_6H_5CHO + NCCH_2CO_2C_2H_5 \xrightarrow[EtOH,\ KF]{reflux} C_6H_5CH{=}C(CN)CO_2C_2H_5$$

$$CH_3COC_2H_5 + NCCH_2CO_2C_2H_5 \xrightarrow[EtOH,\ KF]{40\text{-}50^\circ C,\ 20\ h} CH_3(C_2H_5)C{=}C(CN)CO_2C_2H_5$$

$$CH_2O + CH_2(CO_2C_2H_5)_2 \xrightarrow[EtOH,\ KF]{45^\circ C,\ 4\ h} CH_2\begin{matrix}CH(CO_2C_2H_5)_2\\ CH(CO_2C_2H_5)_2\end{matrix}$$

Fukui and Kitano reported that C-alkylation of active methylene compounds and N-alkylation of aniline and nuclear-substituted anilines by alkyl halides were successfully carried out by using potassium fluoride as the condensing agent.[7] They recommended this method for the preparation of N-monoalkyl and N,N-dialkyl derivatives of aniline and nuclear-substituted anilines. Satoshi Kame used potassium fluoride as the catalyst in the Michael addition of nitroalkanes to α,β-unsaturated compounds.[8] Acrylonitrile reacted with a series of nitroalkanes in alcohol within several hours with heating. Patterson extended this work using acrylamide as Michael acceptor and found potassium fluoride gave better yields,

simpler reaction conditions than the other common bases (such as potassium hydroxide or liquid ammonia) at room temperature.[9] Most aldehydes react

$$CH_3NO_2 + 3CH_2{=}CONH_2 \longrightarrow O_2NC(CH_2CH_2CONH_2)_3$$

$$C_6H_5CH_2NO_2 + 2CH_2{=}CHCONH_2 \longrightarrow C_6H_5C(NO_2)(CH_2CH_2CONH_2)_2$$

with nitroalkanes in the presence of base to give the next higher polymers, or mixtures of them; but only provide a very poor yield of nitroalcohol.[10] Kambe and Yasuda found that, in the presence of potassium fluoride, reaction of nitroalkanes with aldehydes gives a higher yield of nitroalcohols.[11]

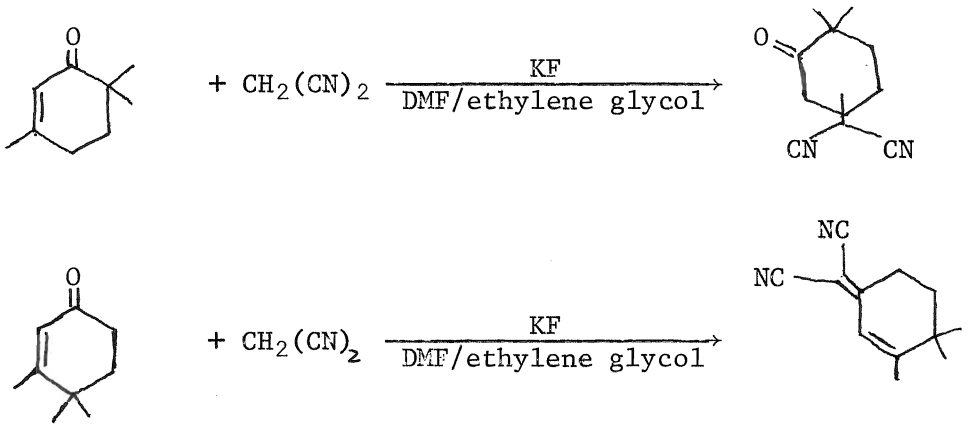
$$CH_3CH_2NO_2 + H_2CO \xrightarrow[KF]{50°C,\ 6\ h} CH_3\underset{\displaystyle NO_2}{\underset{|}{C}}HCH_2OH$$

$$CH_3CH_2NO_2 + CH_3CHO \xrightarrow[KF]{50°C,\ 6\ h} CH_3\underset{\displaystyle NO_2}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}HCHOH$$

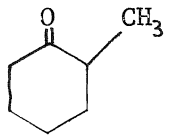
In the investigation of the effect of potassium fluoride on the alkylation of several malonic esters with benzyl chloride, Sen and Sarma found that, in the presence of potassium fluoride, the alkylation reactions are quite effective. A mixture of diethyl malonate, potassium fluoride and benzyl chloride refluxed 8 hours in ethanol gave 68% diethyl benzylmalonate.[12]

$$C_6H_5CH_2Cl + (C_2H_5)O_2CCH_2CO_2(C_2H_5) \xrightarrow[8\ h,\ reflux]{KF/ethanol} (C_2H_5)O_2C\underset{\displaystyle C_6H_5}{\underset{|}{\overset{\displaystyle CH_2}{\overset{|}{C}}}}HCO_2(C_2H_5)$$

Attempts to induce a Michael addition of diethyl malonate to substituted 2-cyclohexenone in the presence of various bases failed, but ApSimon used potassium fluoride in the reaction and found some interesting results.[13] If the carbonyl group of the α,β-unsaturated ketone is hindered, Michael addition occurs. In the other case, when the carbonyl group of the α,β-unsaturated ketone is not hindered, a Knoevenagel reaction appeared to occur first followed by intramolecular condensation.[13]

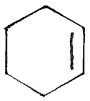
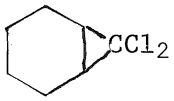


Besides these condensation reactions and addition reactions, fluoride ion can also be used in oxidation reactions and elimination reactions. Chafetz reported that selective oxidation of α-hydrocarbon-substituted cyclohexanones occurs in the presence of potassium fluoride, cesium fluoride or rubidium fluoride.[14] A mixture of 2-methyl cyclohexanone and potassium fluoride was heated and oxygen gas bubbled through the solution several hours to give an oxidation product. Less than 1% oxidation product was isolated when the oxidation took place without potassium fluoride. Dihalocarbene is usually generated from haloform with



$$\xrightarrow[139°C,\ 5\ h]{2.4\ \ell/min\ O_2,\ KF} CH_3COCH_2CH_2CH_2CH_2CO_2H$$

sodium hydroxide.[15] Hayami found that dichlorocarbene can also be generated from haloform with tetraethylammonium fluoride.[16] To the mixture of cyclohexene and tetraethylammonium fluoride, chloroform was added and stirred overnight at room temperature, 20% dichloronorcarane was obtained.

$$CHCl_3 + \text{  } \xrightarrow[CH_3CN/\text{room temperature}]{(CH_3CH_2)_4\overset{+}{N}\ F^-} \text{  }$$

He also reported that the reactivity of the fluoride salt is lost if the reaction mixture is contaminated with water. β-Elimination can also be promoted by fluoride ion. Styrene was produced in an excellent yield by the reaction of β-phenylethylbromide with tetraethylammonium fluoride at room temperature.[17]

$$C_6H_5CH_2CH_2Br \xrightarrow[CH_3CN]{(CH_3CH_2)_4\overset{+}{N}\ F^-} C_6H_5CH{=}CH_2$$

Strong hydrogen bonds in organic synthesis

In a search for a solvent which can separate potassium fluorosulphite from potassium fluoride, Emsley discovered that potassium fluoride dissolves in acetic acid very readily.[18] Since only a few solvents dissolve even a small amount of alkali metal fluoride, he followed up this observation and found out that several simple alkali metal fluorides have exceptionally high solubility in acetic acid, for example, 280 g potassium fluoride in

1000 g acetic acid,[18] and these fluorides dissolved with the evolution of heat. He suggested that the hydrogen bond was the key to these unexpected observations. That is, fluoride ion forms a hydrogen bond to the acid hydroxyl hydrogen. This is not surprising since halide ions such as chloride and bromide have been reported to form hydrogen bonds with acetic acid.[19] His suggestion was supported by infrared studies, proton magnetic resonance studies and thermodynamic studies.[20] In the infrared spectra of potassium fluoride-acetic acid monosolvate and cesium fluoride-acetic acid monosolvate, the -OH stretching frequency was shifted about 2200 cm^{-1} from that of acetic acid monomer at 3600 cm^{-1}.[20,21] In the proton magnetic resonance, the chemical shift of the hydroxyl group, δ(OH), of these monosolvates was found at 17.39 ppm.[20,22] The bond enthalpy of this hydrogen bond was estimated thermodynamically to be ca. 120 kJ mol^{-1}. More recent studies[20] have suggested that the true value for $\Delta H°$ may well lie near 220 kJ mol^{-1}.[23]

Since potassium fluoride is soluble in acetic acid, it was thought that such a system might offer a convenient route to the fluorination of organic compounds in a homogeneous system. In an attempt to prepare chloroacetic acid, Clark and Emsley found a surprising result. In the reactions of potassium fluoride and chloroacetic acids, polymerization took place along with lactonization and elimination reactions.[24] These

$$ClCH_2CO_2H + KF \longrightarrow ClCH_2CO_2CH_2CO_2H$$

$$ClCH_2CH_2CH_2CO_2H + KF\text{-}CH_3CO_2H \longrightarrow \overline{OCH_2CH_2CH_2CO}$$

$$CH_3CHClCH_2CO_2H + KF\text{-}CH_3CO_2H \longrightarrow CH_3CH{=}CHCO_2H + CH_3\underset{\displaystyle O_2CCH_3}{\underset{|}{C}}HCH_2CO_2H$$

results showed that the fluoride-acetic acid system is a good acetoxylating agent rather than a fluorinating agent. In these reactions, they did not consider that fluoride ion acted as a base. Since fluoride ion can form a hydrogen bond with acetic acid, they considered fluoride ion as an electron donor which acts, via the hydrogen bond, to transfer electrons to the organic part of the complex. This will lower the nucleophilicity of the fluoride ion and increase the nucleophilicity of the organic molecule and changes the course of the reaction. In this fluoride-acetic acid system, the nucleophilicity of the hydroxyl oxygen atom of the carboxylic acid was increased by this phenomenon.[24]

This discovery provided a way to enhance the reactivity of some organic molecules capable of acting as hydrogen bond electron acceptors in the reaction. Clark and Miller found a number of aromatic compounds such as phenols and aniline and benzene thiol, can form strong hydrogen bonds with fluoride and rapidly react with alkyl halides producing condensation products.[25] They also found that these reactions were often more rapid and may provide higher yields than the standard methods for the corresponding condensation products.[25] Some examples are given below for comparison.

$$C_6H_5OH + CH_3CH(Cl)CO_2H \xrightarrow[130°C/0.5\ h]{KF} CH_3CH(OC_6H_5)CO_2H \qquad (95\%)$$

$$RC_6H_4OH + CH_3CH(Cl)CO_2^-Na^+ \xrightarrow[8\ h]{} CH_3CH(OC_6H_4R)CO_2H \qquad (30\%)$$

$$C_6H_5SH + CH_3CH(I)C_2H_5 \xrightarrow[130°C/0.5\ h]{KF} CH_3CH(SC_6H_5)C_2H_5 \qquad (92\%)$$

$$C_6H_5S^-Na^+ + CH_3CH(Br)C_2H_5 \xrightarrow[120°C/24\ h]{} CH_3CH(SC_6H_5)C_2H_5 \qquad (45\%)$$

Most β-dicarbonyl compounds exist as a mixture of keto-enol tautomers. When the equilibrium concentration of the enol tautomer is relatively high,

attempted C-alkylation of a β-diketone or indeed any enolisable β-dicarbonyl compounds may also produce significant amounts of the O-alkylated product. Many attempts have been made to improve the yield of the C-alkylated products. From many observations, it would seem that O-alkylation may be inhibited by careful control of conditions or by shielding the oxygen atom by association with a metal cation or with a hydrogen bonding solvent.[26] The utilisation of thallium (I) enolates proved to be very successful giving exclusively mono-C-alkylated product on treatment with short chain alkyl halides.[27] This method suffers from prolonged reaction periods. Miller and Clark found that, from the proton magnetic resonance spectrum of the β-diketone-tetraethylammonium fluoride monosolvate, the β-diketone is totally enolised.[28] The treatment of this monosolvate with alkyl halides also gave a high yield of mono-C-alkylated product with no apparent O-alkylated product or other side reaction. Compared with thallium (I) enolates, fluoride-β-diketone systems required milder conditions. Extending the work to the preparation of α-thio-β-dicarbonyl[29] and methylenation of catechols,[30] they also found the hydrogen bond-assisted reactions gave better results. It is believed that the reactions described in the previous section, such as condensation reactions, or addition reactions, are examples of hydrogen bond assisted reactions.

Scholdenger and Allerhand reported that fluoride ion can form a hydrogen bond with methanol.[31] And in a far- and mid-infrared study, Bacelon, Corset and De Loze found that there is a hydrogen bond between fluoride ion and phenol.[32] In this work, studies have been made on the preparation of phenacyl esters, the esterification of carboxylic acids, the alkylation of phenols and alcohols and the reaction of benzyl halides with 2-nitropropane using fluorides to promote these reactions. The

sources of the fluoride ion used were alkali metal fluoride, tetraethylammonium fluoride and polymer immobilised fluorides. The products, if any were obtained, were identified by mass spectroscopy, infrared spectroscopy and proton nuclear magnetic resonance. This thesis will report and discuss the results of these reactions.

Chapter II

The preparation of phenacyl esters

Introduction

In organic chemistry, phenacyl esters provide means for characterising organic acids and can be used as protecting groups. In a study of the known derivatives of phenacyl alcohol, Rather and Raid suggested that its ester might be of use for identification of acids.[33] Phenacyl bromide reacts with sodium salts of organic acids and gives products which, usually, are solids. Thus many phenacyl esters and p-substituted phenacyl esters of organic acids have been prepared for the purpose of characterisation.[34]

Hendrickson and Kandall reported that phenacyl esters can be used as protecting groups for acids and phenols.[35] They are formed easily and selectively. The most important fact is that they are stable to many reaction conditions used in organic synthesis and are released under very mild conditions.[35] They can be removed by treatment of the derivative with zinc in acetic acid at room temperature.[35]

Phenacyl esters can be prepared according to the tranditional method.[36] To the mixture of carboxylic acid and a 10% sodium hydroxide solution, phenacyl bromide or p-substituted phenacyl bromides are added and are heated under reflux for one hour.[36] The other method is to treat the sodium salt of the acid with phenacyl bromide in alcohol.[36] There are several disadvantages in the traditional methods. The presence of alkali in the reaction

$$RCO_2H + C_6H_5COCH_2Br \xrightarrow[\Delta]{10\%\ NaOH} RCO_2CH_2COC_6H_5$$

$$RCO_2^-Na^+ + C_6H_5COCH_2Br \xrightarrow[C_2H_5OH]{} RCO_2CH_2COC_6H_5$$

mixture causes hydrolysis of the phenacyl bromide to phenacyl alcohol.[37] Pokras and Bernstein found that, in the presence of excess amounts of sodium chloride present to inhibit hydrolysis, p-bromophenacyl bromide always gives p-bromophenacyl chloride under the conditions generally used to prepare the phenacyl ester.[38] Even when equimolar quantities of phenacyl bromide and sodium chloride were used, partial conversion was still observed.[38] Furthermore, the traditional methods are slow, provide low yields of product, and contamination of product with starting material is observed.[36]

Durst attempted this reaction using the potassium salt of an acid and dicyclohexyl-18-crown-6 or 18-crown-6 as solubilizing catalyst under reflux conditions and found that doing this gives high yield and overcomes the problems which occur in the traditional methods.[39] The advantages of using crown ether as a solubilizing catalyst to prepare phenacyl ester are that they always give quantitative yields and no side products are obtained. The disadvantage is that crown ethers are quite expensive. Recently, Miller and Clark reported a simple, inexpensive and efficient way to prepare phenacyl ester by using potassium fluoride in carboxylic acids which has been followed up in this work.[40]

Experimental

Materials

Potassium fluoride was a commercial sample dried at 100°C *in vacuo* for several hours. Tetraethylammonium chloride was a commercial sample, dried at 100°C *in vacuo* for 2 hours. Analytical grade N,N-dimethylformamide was dried over molecular sieves as were analytical grade acetic acid and dichloroacetic acids. Phenacyl bromide, p-phenylphenacyl bromide and carboxylic acids were commercial materials used as obtained, without further purifications.

Reactions

The technique used in each case was the same. Experimental details for one representative preparation are given below:

Preparation of phenacyl acetate

Phenacyl bromide (0.01 mole) was stirred with a mixture of potassium fluoride (0.02 mole) and acetic acid (0.01 mole) in N,N-dimethylformamide (10 g) at room temperature. After 30 minutes, the reaction was stopped and the reaction mixture was extracted into diethyl ether. The ethereal extracts were washed three times with equal volumes of water to remove N,N-dimethylformamide, dried (magnesium sulphate) and evaporated to give a slightly yellow solid. The solid was purified by recrystallization using absolute alcohol as the solvent and gave a white crystalline material; m.p. 48-49° (Lit., 51-52,[43] 49[44]) δ 2.24 (s, 3H); 5.36 (s, 2H) and δ = 7.75 (m, 5H), m/e = 178

Results and Discussion

The products of the reactions of phenacyl bromide or p-phenylphenacyl bromide with carboxylic acids in the presence of potassium fluoride were solids. The proton magnetic resonance spectra of the isolated products when compared with that of phenacyl bromide showed no starting material present. A new peak was observed at lower field and its chemical shift value was dependent on the carboxylic acid. Integrating the peak indicated that it represented two protons. The infrared spectra of the isolated products showed bands due to two carbonyl groups. As compared with the starting material, one is assigned for the phenacyl group, one is for the carboxylate group. One peak at 1235 cm^{-1} was common to all the infrared spectra. This was assigned to the C-O stretching of an ester. The mass spectra of these isolated products showed the expected parent peak, M^+ = molecular weight of the compound, although the p-nitrobenzoate derivative showed (M^+-NO) as the highest mass peak. From this data, it is clear that the products of the reactions are phenacyl esters of the corresponding acids. The attempted reactions and the results are summarized in Table I. The yields of the reactions are nearly quantitative and the reactions were completed within one to two hours at room temperature.

The formation of phenacyl ester is a nucleophilic substitution reaction. It can be explained in the following equations. Fluoride ion forms a strong hydrogen bond with carboxylic acid and gives a fluoride-

Table I Formation of phenacyl and p-phenylphenacyl esters of carboxylic acids[a]

Acid	phenacyl ester			p-phenylphenacyl ester		
	time (h)	yield[b] (%)	m.p. (°C)	time (h)	yield (%)	m.p. (°C)
CH_3CO_2H	0.5	60	48-49° (51-2°)[43] (49°)[44]	0.5	75	108-109° (111°)[45]
$(CH_3)_3CCO_2H$	1.0	60	57-58° (61-62°)[43]	1.2	71	106-108° (113-114°)[42]
$ClCH_2CO_2H$	0.4	78	109-110°	--	--	--
Cl_2CHCO_2H	0.25	87	43-44°	0.4	75	116-118°
$CH_2=CHCO_2H$[c]	0.75	90	--	1.0	82.5	72-74°
$C_6H_5CO_2H$	2	83	120-121° (119°)[33]	1.5	70	167-168° (167°)[34]
$p\text{-}NO_2C_6H_4CO_2H$	1.5	80	130-132° (129°)[33]	1.0	7.5	183-184° (182°)[45]

[a] All the reactions were carried out in N,N-dimethylformamide at room temperature unless otherwise indicated.

[b] Isolated yield

[c] $CH_2=CHCO_2CH_2COPh$ is a liquid

$$RCO_2H + KF \longrightarrow (RCO_2...H...F)^-K^+$$

$$(RCO_2...H...F)^-K^+ + PhCOCH_2Br + KF \longrightarrow RCO_2CH_2COPh + KBr + KHF_2$$

carboxylic acid anionic complex. This anionic complex attacks phenacyl bromide to replace bromide ion and forms the phenacyl ester. Potassium bromide and potassium hydrogen bifluoride are the by-products of reaction. No fluorination is observed in the course of the reaction.

From Table I, it can be seen that α-substituents at the acids slightly affects the reaction. It has been reported that an α-substituent at the acid affects the hydrogen bonding ability of the acid.[41] In the reactions of carboxylic acids with dichloroalkanes in the presence of potassium fluoride and in the studies of cesium fluoride in carboxylic acids, propanoic acid was found to have a hydrogen bonding ability that is slightly weaker than acetic acid and it takes a longer time to complete the reaction.[22,41] Since the reactions were carried out at room temperature under the same conditions, the time needed to complete the reaction may reflect the hydrogen bonding ability of the acids. Chloroacetic acid and dichloroacetic acid are stronger than acetic acid in terms of hydrogen bonding ability. Trimethyl acetic acid and acrylic acid are slightly weaker. p-Nitrobenzoic acid is better than benzoic acid. Also, it seems that aliphatic acids are stronger than aromatic acids. This observation can be explained as follows. It is believed that a strong hydrogen bond is formed between fluoride ion and carboxylic acid. Through this hydrogen bond, fluoride ion transfers electron density to the organic molecule. As a result, it increases the nucleophilicity of the organic molecule and accelerates the reactions. Any factors which affect the transfer of the

electron density from fluoride ion to the organic part would affect the nucleophilicity of the organic molecule and, then, slow down the reaction. A chlorine atom attached to an organic molecule is recognized as an electron withdrawing group. In chloroacetic acid, it pulls electron density away from the -COOH. This helps fluoride ion transfer electron density easily to the oxygen atom of the -COOH. In trimethylacetic acid, the methyl groups donate their electrons to the -COOH; this does not help the fluoride ion to transfer its electrons to the oxygen atom of the -COOH, and thus it weakened the hydrogen bond. As a result, its hydrogen bonding ability is less than that of acetic acid. In aromatic acids, the π electrons of the benzene ring could be delocalized with the non-bonding electrons of the carbonyl group, and as a result, the electron density at -COOH could be slightly higher than at -COOH in aliphatic acids. This makes fluoride ion less able to donate electrons to the -COOH, and thus weakens the hydrogen bond. Indeed, the fluoride-benzoic acid hydrogen bond is weaker than that of the fluoride-acetic acid.[25] If we consider acrylic acid as between acetic acid and benzoic acid, this electron delocalization factor can be easily seen. The degree of electron delocalization of acrylic acid is less than that for benzoic acid, so it is slightly more reactive than benzoic acid. The use of p-substituted phenacyl bromide in place of phenacyl bromide did not affect the reaction very much, but p-substituted phenacyl bromide always gives a solid, which helps to identify the acids and it is an easy derivative to separate.

It has been reported that chloride ion can form a hydrogen bond to acetic acid.[19] In order to examine the utility of this hydrogen bond in organic synthesis, tetraethylammonium chloride was used to replace

potassium fluoride in the reaction. A mixture of tetraethylammonium chloride, phenacyl bromide and acetic acid was stirred at room temperature for two hours and then separated. A solid was isolated which has a melting point at 49-53°C. The proton magnetic resonance spectrum of this solid is similar to that of phenacyl chloride. The mass spectrum of this solid indicated it was phenacyl chloride along with some phenacyl bromide. Therefore, the weaker chloride-acetic acid hydrogen bond has less effect on the nucleophilicity of the consitutuent species and the chloride ion remains an effective nucleophile enabling halide exchange to occur.

One interesting thing was observed during investigations of the synthesis of phenacyl esters. Phenacyl bromide reacts in N,N-dimethylformamide in the presence of potassium fluoride. A mixture of phenacyl bromide and potassium fluoride was heated with stirring in dimethylformamide at 100°C for 30 minutes. The colour of the solution changed from pale yellow to orange. Prolonged heating of the mixture led to a red solution. After separation, a deep red liquid was isolated. The data from proton magnetic resonance and mass spectroscopy indicated that two or more molecules of phenacyl bromide had condensed together with loss of hydrogen bromide. No further investigation was made at this time.

Chapter III

Esterification of carboxylic acids

Carboxylic esters can be prepared in many different ways. In general, they are prepared from the reaction of carboxylic acids with alcohols, or from salts of carboxylic acids and alkyl halides.[46] The product of refluxing a carboxylic acid and an alcohol for a certain period of time is an ester. This method is efficient for the preparation of an ester from a carboxylic acid and a primary alcohol. The yields of esters from secondary alcohols are only reasonable. Tertiary alcohols and phenols do not react, to any appreciable extent, with carboxylic acids.[46] The presence of a small amount of catalyst in the system always makes the esterification more efficient. Usually, sulfuric acid, hydrochloric acid or aryl sulfonic acid are used as catalysts for preparing some simple esters.[46] Sometimes, special kinds of catalysts are used for some esterifications. Boron trifluoride is used as the catalyst in the preparation of esters of substituted benzoic acids.[47] Trifluoroacetic anhydride has been used very successfully as the catalyst for esterification of hindered acids.[48] Boron trifluoride etherate-alcohol mixture is a better catalyst than boron trifluoride gas in the esterification of carboxylic acids.[49a-c] In the presence of 1-methyl-2-halopyridinium iodide and a base, such as tributylamine, the reactions of the carboxylic acids and the alcohols always give high yields of esters.[50] Esters of tertiary alcohols and of phenols can be prepared by using acid halides instead of carboxylic acids in the above reaction.[46]

Alkyl halides are converted to esters by treatment with the salts of carboxylic acids in suitable solvents. It is difficult to find a common

solvent for both the salt and the alkyl halide, so this method is of little preparative value. Low yields are another disadvantage of this method. Even though the utilisation of silver salts is more effective, they are too expensive for larger than laboratory scale work.[46] Since activated halides, such as p-nitrobenzyl chloride and phenacyl bromide, are converted to esters through reaction with trimethylamine carboxylate, Merker and Scott used tertiary amines as catalysts for preparation of esters from alkyl halides and carboxylic acids in appropriate solvents and the results were quite satisfactory.[51] One problem arising from this synthesis is that certain types of alkyl halides react with the tertiary amine to form the quaternary ammonium halide in the reaction, thus lowering the yields of esters. Later, Mills modified the synthesis and obtained higher yields.[52] Pfeffer found that sterically hindered acids can be easily esterified under alkaline conditions using alkyl halides in ethanol with hexamethylphosphoric triamide as cosolvent.[53] Shaw also found that hexamethylphosphoric triamide is a good solvent for esterification.[54]

With the advent of crown ethers, it is possible to produce a naked anion as a reactive intermediate in a reaction system. Liotta observed that acetates solubilized as the potassium salts in benzene containing 18-crown-6 become sufficiently nucleophilic to react with a wide variety of alkyl halides to give esters.[55] Carboxylic acid can be converted to ester at room temperature by the reaction with alkyl halides in the presence of a phase transfer catalyst.[56] Based on the principle of phase transfer catalysis, Cainelli used an anionic-exchange resin to prepare esters from a carboxylic acid and alkylating agents and obtained satisfactory results.[57]

Since we have shown that reactions of phenacyl bromide and carboxylic acids in the presence of potassium fluoride give encouraging results, it was

decided, therefore, to investigate less reactive halogen compounds to further determine the utility of the hydrogen bond in organic synthesis.[40]

Experimental

Materials

Potassium fluoride was commercial grade, dried at 100°C *in vacuo* for two hours. AnalaR carboxylic acids and N,N-dimethylformamide were dried over 5 Å molecular sieves. Other reagents were generally commercial grade samples, used without further purification.

Reactions

The technique used in each case was the same. The progress of all reactions was monitored by proton magnetic resonance spectroscopy. Details of a representative preparation are given below:

Preparation of benzyl acetate

Benzyl chloride (0.01 mol), acetic acid (0.01 mol), and potassium fluoride (0.02 mol) in 20 ml N,N-dimethylformamide were heated at 100-110°C with stirring. The reaction was stopped after 1 hour at which point proton magnetic resonance analysis showed no starting material remaining. The reaction mixture was extracted into diethyl ether, washed with water, dried (magnesium sulfate) and evaporated to remove the ether. The product was purified on a column of silica gel, using hexane as eluant and gave benzyl acetate (1.3 g, 86%) n_D^{24}= 1.5006 (Lit. value: n_D^{25} 1.5232,[42,60] 1.5242;[61,62] 1.4994[52]); δ = 2.1 (s, 3H), 5.14 (s, 2H), 7.38 (s, 5H); 1740 cm^{-1} (C=O stretching), 1230 cm^{-1} (CO-O stretching), m/e 150.

Results and Discussion

When benzyl chloride and acetic acid were refluxed for six hours, no reaction occurred. This is due to the weak nucleophilicity of the carboxyl group. In the presence of potassium fluoride, benzyl chloride and acetic acid were heated in N,N-dimethylformamide at 100-110°C for one hour and a quantitative yield of benzyl acetate was obtained. That is due to the formation of a hydrogen bond between the fluoride anion and acetic acid which effectively accelerates the reaction. Several carboxylic acids were used in the reaction to prepare the esters. The results are summarized in Table II.

When the reaction was carried out at room temperature using benzyl chloride as alkylating reagent, only 6 to 10% esterification was observed. When benzyl bromide was used, the reactions were 100% completed within two to four hours. The difference is due to the different reactivity of benzyl halides. According to the reactivity order of the halogen, I > Br > Cl, the reactions will be completed in a shorter time if benzyl iodide is used. Compared to the results with those for the phenacyl ester, benzyl halides are less reactive. Even though they are less reactive, no benzyl fluoride was observed in the reactions of benzyl halides studied. Except for chloroacetic acid, no other side reaction was observed. In the case of chloroacetic acid, the result was different from that for the other acids. A brown liquid was isolated, its proton magnetic spectrum was more complicated than expected. Along with benzyl chloride and benzyl chloroacetate, other esters were formed. It has been reported that chloroacetic acid in

Table II. Esterification of carboxylic acids[a]

Acid	Alkyl halide	Time (h)	Yield[b] (%)	$n_D^{25°}$
CH_3CO_2H	$C_6H_5CH_2Cl$[c]	3	6[d]	
	$C_6H_5CH_2Br$[c]	2	85	1.5006 (1.4998)[51]
	$C_6H_5CH_2Cl$	1	80	
$(CH_3)_3CCO_2H$	$C_6H_5CH_2Cl$	1	80	1.4830
$CH_2=CHCO_2H$	$C_6H_5CH_2Cl$	1	87	1.5168
	$C_6H_5CH_2Br$[c]	2.75	83	
$CH_3(CH_2)_{12}CO_2H$	$C_6H_5CH_2Cl$[e]	4	50	1.4798 (1.4803)[63]
$C_6H_5CO_2H$	$C_6H_5CH_2Br$[c]	3.2	86	1.5679 (1.5680)[51]
	$C_6H_5CH_2Cl$	1	70[e]	
$p\text{-}NO_2C_6H_5CO_2H$	$C_6H_5CH_2Cl$[f]	1	75	
2,3,6-trimethyl-benzoic acid	$C_6H_5CH_2Cl$	4	80	1.5371
p-methoxy-benzoic acid	$C_6H_5CH_2Cl$	2	72	1.5732

[a] All the reactions were carried out in N,N-dimethylformamide at ca. 100-110°C unless otherwise indicated

[b] Isolated yield

[c] At room temperature

[d] Based on n.m.r. measurement

[e] M.p. < 23°C (lit. 20.5°C)[62]

[f] M.p. = 85-87°C (lit. 88-89°C)[42]

the presence of potassium fluoride at 150°C gives polymeric products such as (chloroacetoxyl) acetic acid, $ClCH_2CO_2CH_2CO_2H$; and 8-chloro-4,7-dioxy-3,6-dioxaoctanoic acid, $(ClCH_2CO_2(CH_2CO_2)_2CH_2CO_2H)$.[24] In this case, because of the low reactivity of benzyl chloride, it is possible that (chloroacetoxyl)-acetic acid or higher polymeric products are formed, then react with benzyl chloride to give esters leaving the excess benzyl chloride in the solution. When benzyl bromide was used so that the reaction was carried out at room temperature, the proton magnetic resonance spectrum of the isolated product showed only benzyl chloroacetate and benzyl(chloroacetoxy)acetate along with benzyl bromide.

From Table II, it can be seen that all reactions were 100% completed within one to four hours and gave quantitative conversion yields. 2,4,6-Trimethylbenzoic acid, and myristic acid needed longer to complete the reactions. This effect could be due to steric hindrance. In addition to this factor, the inductive factor, which was discussed in the previous chapter, may be important in the cases of 2,4,6-trimethylbenzoic acid and p-methoxybenzoic acid. Recently, Horiki used the same method described here to prepare the Merrifield resin esters of N-protected amino acid and had quantitative yields.[58] In general, our method provides a simpler, more convenient way for the synthesis of esters and affords high yields. However, like the other methods mentioned previously, ours has its disadvantages. It limits the alkylating reagent only to aliphatic halides. No reactions were observed between aryl halides and carboxylic acids in the presence of potassium fluoride.[59] This is due to the low reactivity of aryl halides. Unless more reactive halogen compounds are used, halogen substituted carboxylic acids can not be used, since more complicated reactions would occur.

The reaction is believed to be a nucleophilic substitution reaction. The fluoride-carboxylic acid anionic complex is formed first and replaces the halide ion giving the esters. All the products were identified by their

$$RCO_2H + KF \longrightarrow (RCO_2...H...F)^-K^+$$

$$(RCO_2...H...F)^-K^+ + C_6H_5CH_2X + KF \longrightarrow RCO_2CH_2C_6H_5 + KX + KHF_2$$

$X = Cl, Br$

infrared, proton magnetic resonance and mass spectra data. For details see the characterization of products.

Characterization of products

Benzyl acetate

n.m.r. ($CDCl_3$): δ = 2.10 (s, 3H) 5.14 (s, 2H), 7.38 (s, 5H)

i.r.: 1740 cm^{-1} (C=O stretching), 1230 cm^{-1} (CO-O stretching)

m.s.: m/e = 150 (M^+)

Benzyl trimethylacetate

n.m.r. ($CDCl_3$): δ = 1.24 (s, 9H), 5.12 (s, 2H), 7.35 (s, 5H)

i.r.: 1720 cm^{-1} (C=O stretching), 1140 cm^{-1} (CO-O stretching)

m.s.: m/e = 192 (M^+)

Benzyl myristate

n.m.r. ($CDCl_3$): δ = 0.88 (t, 3H), 1.26 (m, 22H), 2.36 (t, 2H), 5.10 (s, 2H), 7.26 (s, 5H)

i.r.: 1740 cm^{-1} (C=O stretching), 1160 cm^{-1} (CO-O stretching)

m.s.: m/e = 318 (M^+)

Benzyl acrylate

n.m.r. ($CDCl_3$): δ = 5.16 (s, 2H), ca. 6.0 (m, 3H), 7.31 (s, 5H)

i.r.: 1725 cm^{-1} (C=O stretching), 1625 cm^{-1} (C=C stretching), 1180 cm^{-1} (CO-O stretching)

m.s.: m/e = 162 (M^+)

Benzyl benzoate

n.m.r. ($CDCl_3$): δ = 5.34 (s, 2H), 7.38 (s, 5H), ca. 7.80 (m, 5H)

i.r.: 1710 cm^{-1} (C=O stretching), 1260 cm^{-1} (CO-O stretching)

m.s.: m/e = 212 (M^+)

Benzyl p-methoxybenzoate

^{1}H n.m.r. ($CDCl_3$): δ = 2.90 (s, 3H), 5.4 (s, 2H), ca. 7.45 (m, 9H)

i.r.: 2800 cm^{-1} ($-OCH_3$ stretching), 1720 cm^{-1} (CO stretching), 1240 cm^{-1} (CO-O stretching)

m.s.: m/e = 242 (M^+)

Benzyl p-nitrobenzoate

^{1}H n.m.r. ($CDCl_3$): δ = 5.45 (s, 2H), 7.50 (s, 5H), 8.35 (s, 4H)

i.r.: 1710 cm^{-1} (CO stretching), 1525 cm^{-1} ($-NO_2$ stretching), 1275 cm^{-1} (CO-O stretching)

m.s.: m/e = 257 (M^+)

Benzyl 2,4,6-trimethylbenzoate

^{1}H n.m.r. ($CDCl_3$): δ = 2.28 (s, 9H), 5.40 (s, 2H), 6.90 (s, 2H), 7.48 (s, 5H)

i.r.: 1725 cm^{-1} (CO stretching), 1260 cm^{-1} (CO-O stretching)

m.s.: m/e = 254 (M^+)

Chapter IV

Reactions of 2-nitropropane in the presence of tetraethylammonium fluoride

The anion derived from an aliphatic nitro compound is an ambident anion. It is capable of covalent bond formation at either carbon or oxygen. Due to this particular property, the reactions of the salts of the nitro compound with alkyl halides have been studied for a long time.[64-72] Treatment of the sodium, potassium or silver salt of the nitro compound with alkyl halides may result in carbon-alkylation or oxygen-alkylation. The result of the former gives a secondary or tertiary nitro compound. The latter leads to an unstable nitronic ester which cannot be isolated and which breaks down into an oxime and a carbonyl compound. Previous studies showed that only p-nitrobenzyl chloride and 2,4-dinitrobenzyl chloride give carbon-alkylation with the salts of nitro compounds.[64,68] Other halides such as benzyl chloride, p-cyanobenzyl chloride, allylic chlorides and aliphatic chlorides have been reported to produce carbonyl compounds and oximes.[69-73] These data indicated that the reactions of the salts of nitro compounds with alkyl halides and benzyl halides may serve as a means of preparing aldehydes and ketones.

Reaction systems containing both nitro compounds and fluoride ions have provided some surprises in the past. Satoshi Kame reported fluorides were capable of catalyzing the Michael addition of nitroalkanes to α,β-unsaturated compounds.[8] Yasuda also found that nitroalkanes can condense aldehydes to give nitro-alcohols.[11] Yoshikoshi reported that, in the presence of fluoride ion, some of his nitrodione Michael adducts were transformed to triones or to ketofurans.[74]

In primary and secondary nitro-alkanes, the hydrogen directly attached to the nitro carbon is quite acidic which provides a site for hydrogen bonding to fluoride. Through tautomerisation, the aci-form of a nitro-alkane is similar to a carboxylic acid in that it possesses a hydroxyl group which is capable of behaving as a hydrogen bond electron acceptor site. Since fluoride ion can encourage the tautomerization of some active methylene compounds, we decided to investigate the reactions between 2-nitropropane and benzyl halides in the presence of fluoride ion.[28]

Experimental

Materials

Tetraethylammonium fluoride was prepared in aqueous solution by neutralisation of tetraethylammonium hydroxide (commercial samples in aqueous solution) with 48% hydrofluoric acid. p-Nitrobenzyl iodide was prepared by the reaction of p-nitrobenzyl chloride with sodium iodide in acetone at room temperature for several hours and was isolated in 80-90% yields (m.p. 125-127° (lit. 127-128°[42])).

Other benzyl halides were commercial samples used as obtained. 2-Nitropropane and N,N-dimethyl formamide were commercial samples and were dried over 5 Å molecular sieves before use.

Reactions

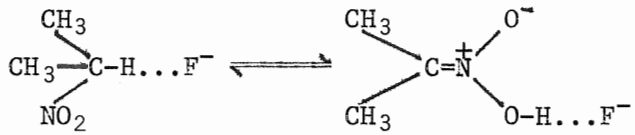
The technique used in each case was the same. Details of a representative preparation are given below:

Preparation of benzophenone

Tetraethylammonium fluoride-2-nitropropane solvate (0.02 mol) was dissolved in N,N-dimethyl formamide (25 ml) and the solution stored at room temperature over molecular sieves. Diphenylbromomethane (0.01 mol) was added and provided an exothermic reaction. White precipitates were formed after 10 minutes. The reaction was stopped after 30 minutes and the resulting mixture was diluted with ether and filtered. The filtrate was washed with water, dried (magnesium sulphate) and evaporated to remove the ether. The product was purified on a column of silica gel, using hexane as eluent and gave benzophenone (1.5 g, 85%), m.p. = 47-49°C (lit. 48-49°[42]) 1640 cm^{-1} (C=O stretching), m/e = 182.

Results and Discussion

To the tetraethylammonium fluoride hydrate, a white solid, excess 2-nitropropane was added and the excess water was evaporated using an aspirator at 80°C for ten minutes; tetraethylammonium fluoride dissolving in 2-nitropropane to give a viscous yellow liquid. The proton magnetic resonance spectrum of this yellow liquid is quite different from that of 2-nitropropane. In addition to the presence of 2-nitropropane and tetraethylammonium fluoride peaks in the spectrum, a sharp singlet, at δ = 1.86 and a broad peak, centered at δ = 5.55 are observed. Compared with the spectral data of the aci-anion of 2-nitropropane, a singlet at δ = 1.90, this sharp singlet may be assigned to the methyl groups of the aci-tautomer of 2-nitropropane.[75] The broad peak may be assigned to the hydrogen bonded N-hydroxyl hydrogen of the aci-tautomer and traces of water which cannot be removed. Also the chemical shift of the -CH of 2-nitropropane shows a slight downfield shift which suggests hydrogen bonding between fluoride and 2-nitropropane.



The relative amount of 2-nitropropane and its aci-tautomer depend on the concentration of fluoride. For example, for a fluoride:2-nitropropane solution with mole ratio of about 3:1, the equilibrium lies in favour of the aci-tautomer, whereas a solution containing about 1:1 mole ratio shows about 20-30% of the aci-tautomer under the same conditions. A N,N-dimethylformamide

solution containing benzyl chloride, fluoride ion and 2-nitropropane in the mole ratio about 1:4:2 was stirred at room temperature for several minutes and heat was evolved. The proton magnetic resonance spectrum of a sample which was taken after the reaction was carried out for fifteen minutes, indicated the benzaldehyde was formed in the solution. The reaction was completed within several hours at room temperature and gave quantitative yields of aldehyde. Benzyl bromide gave the same reaction in a shorter period of time. All the attempted reactions and results are summarized in Table III.

When compared with the previous work, we see that the same results are obtained in our system, though our conditions are much milder. Except for p-nitrobenzyl halides and o-nitrobenzyl chloride, all the other alkyl halides give carbonyl compounds. p-Nitrobenzyl halides and o-nitrobenzyl chloride give a mixture of C-alkylated product and the O-alkylated product. The relative amounts of these products are dependent upon the leaving group. Two mechanisms have been suggested to explain the experimental results. The first one explains the abnormal behaviour of p-nitrobenzyl chloride and of o-nitrobenzyl chloride. From a kinetic study of the reactions of four benzyl halides with lithium 2-propanenitronate, Hass and Bender suggest the nitronic ester is the intermediate in both oxygen and carbon-alkylation.[69] When O-alkylation occurs, a carbonyl compound and an oxime are produced. In the other case a carbanion is formed by the ionization of a benzylic hydrogen of the nitronic ester. Following the ionization, an internal nucleophilic displacement reaction occurs and gives the C-alkylation product. The relative amounts of the final product are determined by the relative rates of the competing cleavage and ionization reactions. Since the ionization step is an equilibrium reaction, thus the factors, such as the reaction medium and the structure of the reactants, which shift the equilibrium will shift the direction of

Table III. The reaction of benzyl halides with 2-nitropropane in the presence of tetraethylammonium fluoride[a]

Benzyl halide	Reaction conditions	O-alkylation (%)	C-alkylation (%)
$C_6H_5CH_2Cl$	reflux/4 hours	75	--
$C_6H_5CH_2Br$	R.T./25 minutes	85	--
$(C_6H_5)_2CHCl$	reflux/1 hour	80[b]	--
$(C_6H_5)_2CHBr$	R.T./20 minutes	82[b]	--
$p\text{-}ClC_6H_4CH_2Cl$	R.T./1 hour	65[c]	--
$p\text{-}NO_2C_6H_4CH_2Cl$	R.T./30 minutes	0	75[d]
$p\text{-}NO_2C_6H_4CH_2Br$	R.T./20 minutes	65[e]	24
$p\text{-}NO_2C_6H_4CH_2I$	R.T./20 minutes	85[e]	16
$o\text{-}NO_2C_6H_4CH_2Cl$	R.T./30 minutes	15[e]	82
$m\text{-}NO_2C_6H_4CH_2Cl$	R.T./30 minutes	73[e]	

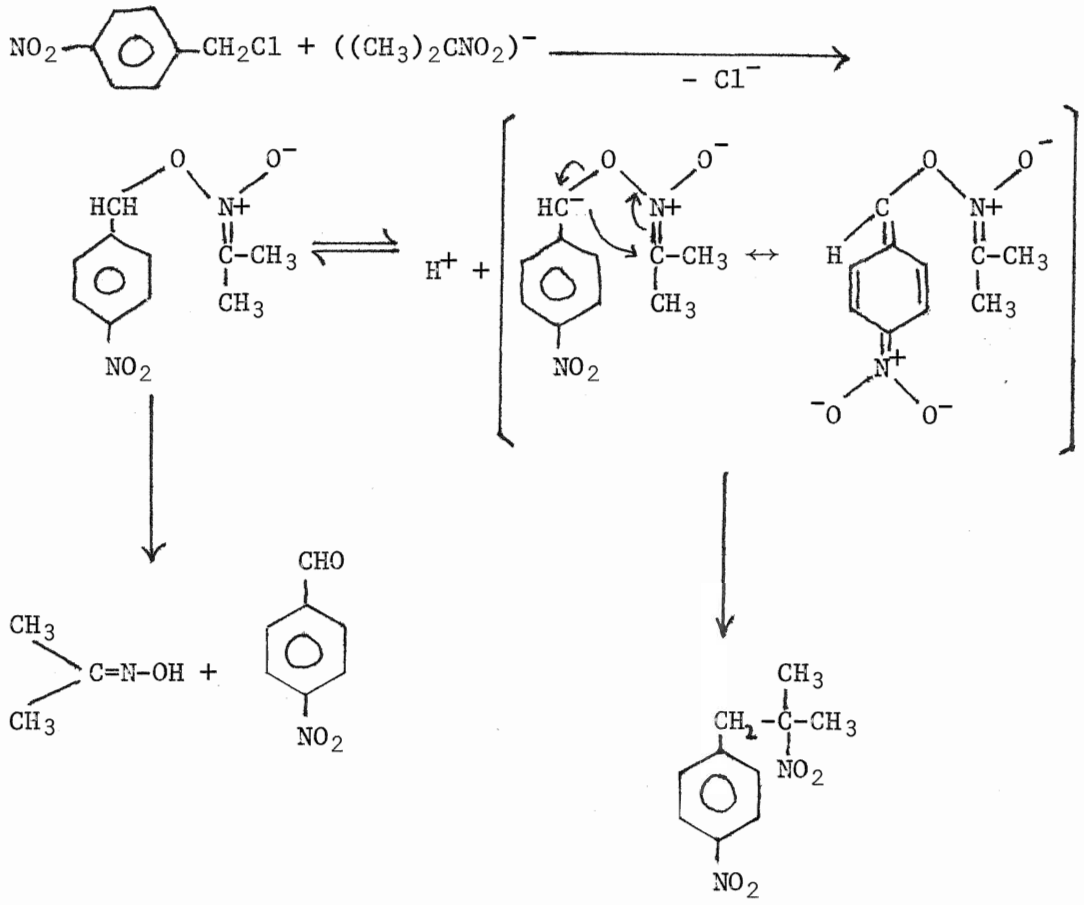
[a] All yields refer to pure products isolated except for the runs employing the p-nitro bromide and iodide, o-nitro chloride; here the yields are by H^1 n.m.r.

[b] M.p. = 47-49° (lit. 48-49°)[42]

[c] M.p. = 66° (lit 65-66°)[42]

[e] Present as the free aldehyde and as the condensation product with 2-nitropropane.

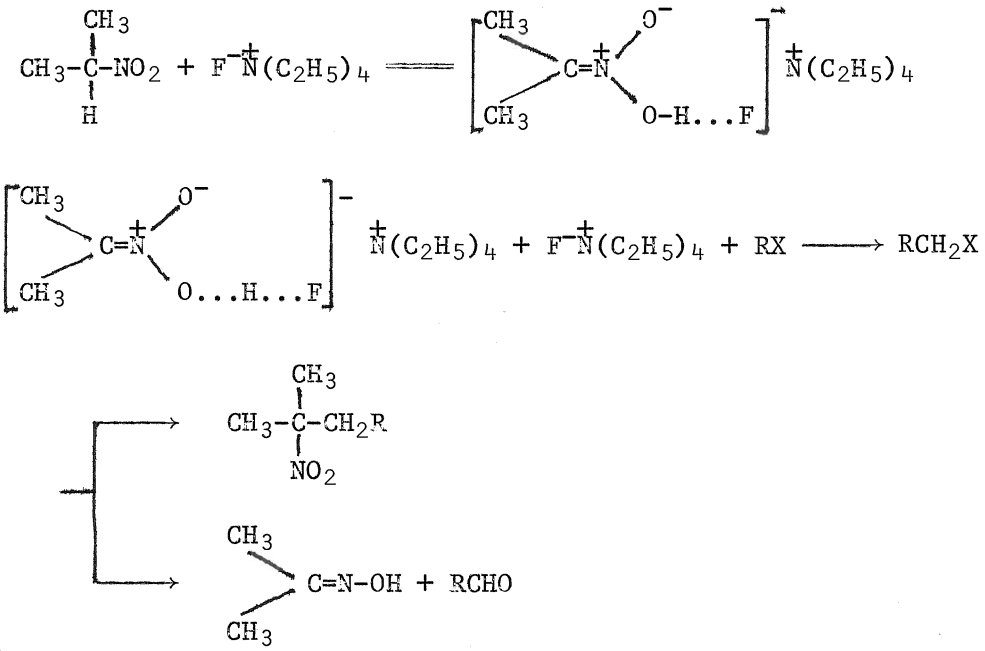
[d] M.p. = 64-65°C (lit. 65-66°)[72]



alkylation. A nitro group at the para- and ortho-positions can increase the ionization of the benzylic hydrogen by inductive effect. Also the nitro group can stabilize the carbanion by resonance effect. Both of these factors shift the equilibrium in favour of the formation of the carbanion and give C-alkylation product.

In a detailed study of the p-nitrobenzyl system, Kornblum observed that the relative amounts of the final product are not only dependent on the nitro group but also on the leaving groups.[72] For example, whereas p-nitrobenzyl chloride gives 95% C-alkylation, the use of p-nitrobenzyl iodide results in 81% O-alkylation. No detailed mechanism is given to explain this leaving group effect. However, he points out that O-alkylation is the usual mode of

reaction of a salt of a nitro compound. It derives simply from nucleophilic displacement by the oxygen of the anion on the benzylic carbon. In the p-nitrobenzyl series, when the leaving group is not an easily displaced group, a second mode of attack by the anion may compete giving the C-alkylation product. Based on this past work, we can suggest a mechanism for the fluoride ion system.



Fluoride ions encourage the tautomerization of 2-nitropropane by stabilising the aci-tautomer by anionic intermolecular hydrogen bonding. This aci-tautomer-fluoride complex reacts with alkyl halides to give the O-alkylation product.

One side reaction is observed in both systems involving the salt of the nitro compound system as well as the fluoride ion system is that prolonging the reaction time causes aldehydes to condense with the nitro compounds to give nitro-alcohols. This nitroalcohol may be converted to the aldehyde in quantitative yield by a short treatment with base. Hass and Bender point out that the preparation of the carbonyl compound, through the reaction of benzyl

halides with the salts of nitro compounds has several advantages.[70] Substances sensitive to oxidation can be converted to carbonyl compounds without recourse to oxidative conditions. Using fluoride ion in this synthesis has advantages over the conventional process involving the lithium or sodium salts of 2-nitropropane, which include brevity and operational simplicity. Reactions employing the metal salts of 2-nitropropane may require a lengthy and tedious initial preparation of the salts and sometimes longer reaction times are needed to complete the reaction.

Chapter V

Preparation of alkyl phenyl ethers

The preparation of alkyl phenyl ethers is an important synthetic reaction for which a wide variety of procedures has been developed during the last hundred years.[76,77] The Williamson procedure is by far the most commonly used

$$ArO^- + RX \longrightarrow ArOR$$

one. The reaction consists of alkylation of the phenoxide ion with an alkylating agent such as halides, sulphate esters or sulphonates. Use of dialkyl sulphate esters as alkylating agents allows both generation and alkylation of phenoxide ion to be carried out in aqueous solution. When alkyl halides are used as alkylating agents, the reactions must be carried out in organic solvents. Usually, the synthesis of the ethers from alkyl halides is efficient, but some care must be taken in the choice of solvent in order to avoid formation of both C- and O-alkylated products.[78,79] In the alkylation of phenoxide ion and β-naphthoxide ion Kornblum found that the solvents can decide the course of an ambident anion reaction.[79] When solutions of the salts of phenol in a wide variety of solvents were alkylated with alkyl halides the ether was the product. These solvents include ether and dimethyl formamide. However, when these reactions were carried out in strongly hydrogen-bonding solvents such as water or trifluorinated alcohols, substantial amounts of C-alkylated products were obtained in addition to ethers.[80]

There are few useful procedures available for the direct synthesis of alkyl phenyl ethers. Direct alkylation with diazomethane is the most widely

used one, but the obnoxious nature of the reagent is the disadvantage of this method.[76] Alkylation has also been accomplished with alkyl orthocarbonate ester,[81] with dialkyl oxalate esters,[82] and by treatment of phenols with alcohols in the presence of dicyclohexyl carbodiimide.[83] Recently, it was reported that phenol and 2-naphthol can be converted to their alkyl ethers by treatment with the corresponding anhydrous alcohol in the presence of diethyl azodicarboxylate and triphenyl phosphine.[84] B. A. Stoochnoff and N. L. Benoiton found that some phenols could be methylated in excellent yield simply on treatment at room temperature with sodium hydride and methyl iodide in either tetrahydrofuran or dimethyl formamide.[85] None of these methods is very general with respect to the variety of alkyl groups which can be introduced into the alkyl phenyl ether, and they have been employed under special circumstances. However, McKillop used phase transfer catalysts to prepare alkyl phenyl ethers under mild conditions and obtained satisfactory results.[86] Based on the same idea, Gelbard and Colanna successfully used a strong basic anion-exchange resin in the synthesis of alkyl phenyl ethers, in 1977.[87]

In the infrared studies, the spectral shifts of the ν OH vibrations of phenols have demonstrated the presence of a hydrogen bond between the anion and the hydroxyl group of the phenol.[32] Recent studies have found a mixture of potassium fluoride and a number of aromatic compounds capable of acting as hydrogen bond electron acceptors reacts with alkyl halides producing the condensed products.[25] Therefore, attempts were made to use fluoride ion to promote the synthesis of alkyl phenyl ethers.

Experimental

Materials

The phenols and the halides were commercial samples used as obtained without further purifications. Tetraethylammonium fluoride was prepared by neutralisation of 20% aqueous tetraethylammonium hydroxide with 48% aqueous hydrofluoric acid.

Reactions

The technique used in each case was the same. Details of a representative preparation are given below.

Preparation of benzyl 2,6-dimethylphenyl ether

An aqueous solution of tetraethylammonium fluoride containing 0.02 mole of the fluoride was concentrated to a white solid by evaporation at ca. 80°C (water bath) under a mild vacuum (aspirator). 2,6-dimethylphenol (0.01 mole) was added and the whole evaporated with shaking for ten minutes. The mixture changed from yellow to slightly purple. To this mixture, benzyl chloride (0.01 mole) in dimethylformamide (ca. 20 ml) was added. The resulting solution was stirred at room temperature. After two hours, the colour of the solution changed to slightly yellow. The reaction was stopped after 18 hours at which point ^{1}H nmr analysis showed no starting material remaining. The reaction mixture was extracted into diethyl ether, washed with water, dried (magnesium sulphate) and evaporated. A yellow liquid was isolated and purified on a column of basic alumina using pentane as eluent to give benzyl 2,6-dimethylphenyl ether.

Benzyl 2,6-dimethylphenyl ether

n.m.r.: δ = 2.31 (s, 6H), 4.82 (s, 2H), 7.02 (s, 3H), 7.45 (s, 5H)

i.r.: 1200 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 212 (H^+)

Results and Discussion

Liquid phenol (1 mol equiv) and anhydrous potassium fluoride (1 mol equiv) were shaken together at room temperature; the mixture became hot. The infrared spectrum of this mixture showed that the -OH stretching of phenol is lost, and a broad peak, centered at 2600 cm^{-1}, is observed. This broad peak could be the -OH stretching of the phenol bound to fluoride ion, the $\Delta\nu_s$(OH) was approximately 900-1000 cm^{-1}. This indicates that a strong hydrogen bond is formed between phenol and fluoride ion, however, it is slightly weaker than the fluoride-carboxylic acid system, which shows a $\Delta\nu_s$(OH) of 2200 cm^{-1}. Because of the low solubility of alkali metal fluoride in organic solvents, it would be more convenient to use tetraethylammonium fluoride, which is soluble in many organic solvents, as a fluoride ion source so that an homogeneous system can be obtained.

When a mixture of phenol, tetraethylammonium fluoride and methyl iodide in N,N-dimethylformamide was stirred at room temperature for ten hours followed by extraction with ether, a pale yellow liquid was isolated. After purification by column chromatography, a colorless liquid was obtained. Comparison of its infrared spectrum with that of methyl phenyl ether, showed that they were almost identical. Its structure was further confirmed by proton nuclear magnetic resonance and mass spectroscopy. The result of this reaction showed that alkyl phenyl ethers may be prepared directly from phenols and alkyl halides in the presence of fluoride ion. Isomeric nitrophenols and isomeric methylphenols were used in the reactions. The results are summarized in Table IV. Most of the reactions were carried out at room temperature

Table IV Preparation of alkyl phenyl ether (ArOR)[a]

Phenol	Alkylating Agent	Ether yield[b] (%)
C_6H_5OH	CH_3I	70
$2\text{-}CH_3C_6H_4OH$	"	75
$2\text{-}O_2NC_6H_4OH$	"	72
$4\text{-}O_2NC_6H_4OH$	"	76
$4\text{-}FC_6H_4OH$	"	80
$2,6\text{-}(CH_3)_2C_6H_3OH$	"	82
$2,4,6\text{-}(CH_3)_3C_6H_2OH$[c]	"	70
$2,4\text{-}(t\text{-}C_4H_9)_2C_6H_3OH$[c]	"	60
$4\text{-}(CH_3)\text{-}2,6\text{-}(t\text{-}C_4H_9)C_6H_2OH$[c]	"	72
C_6H_5OH	CH_3CH_2I	75
$2\text{-}CH_3C_6H_4OH$	"	65
$2\text{-}O_2NC_6H_4OH$	"	72
$4\text{-}O_2NC_6H_4OH$	"	70
$4\text{-}FC_6H_4OH$	"	65
$2,6\text{-}(CH_3)_2C_6H_3OH$	"	40
$2,6\text{-}(CH_3)_2C_6H_3OH$	$(CH_3)_2CHI$	65
C_6H_5OH	$C_6H_5CH_2Cl$	68
$2\text{-}CH_3C_6H_4OH$	"	60
$2\text{-}O_2NC_6H_4OH$	"	83
$4\text{-}O_2NC_6H_4OH$	"	75
$4\text{-}FC_6H_4OH$	"	80
$2,6\text{-}(CH_3)_2C_6H_3OH$[c]	"	80
$2,4,6\text{-}(CH_3)_3C_6H_2OH$[c]	"	68
$2,4\text{-}(t\text{-}C_4H_9)C_6H_3OH$	"	70
2-naphthol	"	85

[a] All the reactions were carried out in N,N-dimethylformamide at room temperature

[b] Isolated yield

[c] At 100°C

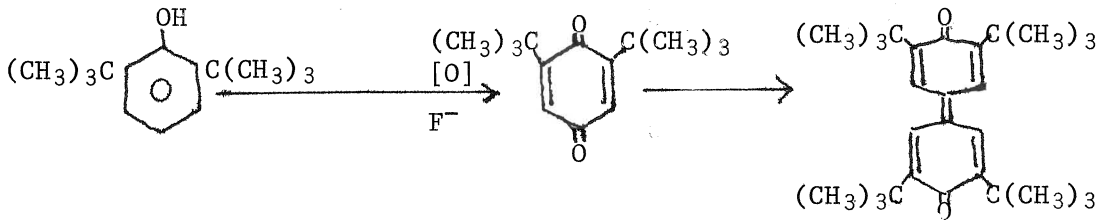
and were completed in 6-24 hours.

The mixtures of the substituted phenols and tetraethylammonium fluoride in dimethylformamide always give coloured solutions. For example, a mixture of 2,6-dimethyl phenol and tetraethylammonium fluoride gave a pale purple solution; 2-methylphenol gave a green one. Stirring these solutions with alkyl halides at room temperature gave the corresponding alkyl phenyl ether. No reaction was observed in control experiments carried out in the absence of tetraethylammonium fluoride. In all the attempted reactions, except 2,6-di-tert-butylphenol, only O-alkylation occurred. No other side reactions, such as fluorination of alkyl halide or C-alkylation, were observed. The presence of a nitro group in the phenol did affect the reaction time, the isomeric nitrophenols needed less time for the reaction to go to completion. On the other hand, the isomeric methyl phenols required longer times to give ethers. Also the ortho-substituted phenols needed more time than the para-substituted phenols because of steric hindrance. It has been reported that the generation of phenoxide ions for some highly hindered phenols is difficult. For example, 2,6-di-tert-butylphenol was reported not to react with either diazomethane or with sodium in boiling ligroin.[88] An attempt was made to prepare the ethers from some highly hindered phenols. Several highly hindered phenols were treated with methyl iodide in the presence of fluoride at room temperature, the yields were low. At higher temperature, about 100°C, higher yields were obtained. Benzylation of 2,6-dimethylphenol, 2,4-di-tert-butylphenol and 2,4,6-trimethyl phenol can be achieved.

In the reaction of methyl iodide and 2,6-di-tert-butylphenol, the final product was analyzed by gas chromatography/mass spectroscopy which showed a mixture consisting of methyl-2,6-di-tert-butylphenyl ether and methyl-4-methyl-2,6-di-tert-butylphenyl ether. In the reactions of 2-iodopropane with

2,6-di-tert-butylphenol and benzyl chloride with 2,6-di-tert-butylphenol, a brown solid was isolated. Its proton nuclear magnetic resonance spectrum indicated that it is not the expected ether, isopropyl-2,6-di-tert-butylphenyl ether and benzyl-2,6-di-tert-butylphenyl ether. The spectrum consisting of two singlets at δ = 1.36 and δ = 7.75, with the ratio 9:1. For the mass spectrum, the compound has a molecular ion at m/e = 408. Its infrared spectrum showed that the compound contains a highly conjugated system and a carbonyl group. It was reported that 2,6-di-tert-butylphenol can be oxidized to give a quinone under basic conditions.[89] Recently, McKillop reported cobalt-dioxygen complex can catalyze the autoxidation of hydroquinones and phenols.[90] Oxidation of 2,6-di-tert-butyl phenol gave the diphenoquinone. Comparing the physical properties and the spectral data with those in the literature, the compound may be 3,3',5,5'-tetra-tert-butyl diphenoquinone.[91,92] The reaction was repeated without alkyl halides in the reaction system, and the same result was obtained. When the reaction was stopped after a shorter time (24 hours), some yellow crystals were isolated from the reaction mixture. The proton magnetic resonance spectrum of these yellow crystals was similar to that of the diphenoquinone. It consisted of two singlets, at δ = 1.28 and δ = 6.70, with ratio 9:1. The compound had a molecular ion at m/e = 220. Again, its infrared spectrum indicated that it contains a highly conjugated system. Comparing the physical data and spectral data with those in the literature, this compound was shown to be 2,6-di-tert-butyl-p-benzoquinone.[91,92] When 2,6-di-tert-butyl-4-methylphenol was stirred with tetraethylammonium fluoride in N,N-dimethyl formamide at room temperature for 48 hours, some yellow crystals were isolated. The product was a mixture and could not be separated and thus the components of the mixture could not be identified. In these reactions, fluoride ion seems to have the ability to catalyze the autoxidation

of the highly hindered phenols. The reaction was repeated, but using 2,6-dimethylphenol and 2,4-di-tert-butylphenol instead of 2,6-di-tert-butyl phenol, under the same reaction conditions. Only the starting phenols were isolated. In another attempt, oxygen gas was bubbled into the phenol and fluoride mixture for a day, but no reaction occurred. Therefore, the autoxidation of phenol occurs only provided bulky substituents such as tert-butyl group are present at the 2,6-positions of the phenol. Similar results were obtained in the autoxidation of hindered 1-alkyl-2-naphthols.[93,94] Only 1-isopropyl, 1-tert-butyl- and 2-tert-pentyl-2-naphthols were found to be oxidized. 1-Methyl and 1-benzyl-2-naphthols did not react with oxygen.[93,94] The mechanism is not clear but it may be that 2,6-di-tert-butyl-p-benzoquinone may be an intermediate in the autoxidation of the phenol.



The formation of alkylphenyl ether is a result of a nucleophilic substitution reaction. Fluoride ion forms an anionic complex with phenol by the formation of a hydrogen bond. Then, this complex may then react with the alkyl halide to give the corresponding ether.

$$C_6H_5O\text{-}H + F^{-}\overset{+}{N}(C_2H_5)_4 \longrightarrow (C_6H_5O...H...F)^{-}\overset{+}{N}(C_2H_5)_4$$

$$(C_6H_5O...H...F)^{-}\overset{+}{N}(C_2H_5)_4 + RX + F^{-}\overset{+}{N}(C_2H_5)_4$$

$$\longrightarrow C_6H_5OR + X^{-}\overset{+}{N}(C_2H_5)_4 + HF_2^{-}\overset{+}{N}(C_2H_5)_4$$

Compared with the conventional methods, the fluoride ion system is better, no conventional strong base is required nor are any special precautions such as a nitrogen atmosphere or controlled addition of reagents needed. The yields, from Table IV, were quite good. Although in some cases, the phase transfer system gave higher yields, no reaction was observed in the case of 2,6-dimethylphenol when either ethyl or isopropyl iodide was substituted for methyl iodide. Since no reaction was observed previously when aryl halide was substituted for alkyl halides in the preparation of ester aided by fluoride ion, therefore no aryl halides were tried as substitutes for alkyl halides in the preparation of ethers.[59] However, Vorozhtsov and Iacobson reported 2,4-di-nitrochlorobenzene and 2,4-dinitrofluorobenzene react with alcohols and phenols in the presence of potassium fluoride giving the corresponding ethers.[95]

Product Characterization

methyl phenyl ether

n.m.r.: δ = 3.82 (s, 3H), 6.75-7.5 (m, 5H)

i.r.: 2830 cm^{-1} (OCH_3 stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching) 1040 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 108 (M^+)

methyl 2-methylphenyl ether

n.m.r.: δ = 2.22 (s, 3H), 3.84 (s, 3H), 6.75-7.5 (m, 4H)

i.r.: 2850 cm^{-1} ($-OCH_3$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching) 1025 cm^{-1} (Ar-O-C symmetric stretching)

m/s/: m/e = 122 (M^+)

methyl 2-nitrophenyl ether

n.m.r.: δ = 3.80 (s, 3H), 7.0- 8.0 (m, 4H)

i.r.: 2480 cm^{-1} ($-OCH_3$ stretching), 1525 cm^{-1}, 1350 cm^{-1} ($-NO_2$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1025 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 153 (M^+)

methyl 4-nitrophenyl ether m.p. 50-52°C

n.m.r.: δ = 3.95 (s, 3H), 7.63 (AA'BB' pattern, 4H)

i.r.: 2835 cm^{-1} ($-OCH_3$ stretching), 1530 cm^{-1}, 1350 cm^{-1} ($-NO_2$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1020 cm^{-1} (Ar-O-C symmetric stretching).

m.s.: m/e = 153 (M^+)

methyl 4-fluorophenyl ether

n.m.r.: δ 3.75 (s, 3H), 6.80-$\sim$7.10 (m, 4H)

i.r.: 2845 cm^{-1} ($-OCH_3$ stretching), 1250 cm^{-1} (Ar-O-C symmetric stretching), 1090 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 126 (M^+)

methyl 2,6-dimethylphenyl ether

n.m.r.: δ = 2.26 (s, 3H), 3.72 (s, 3H), 7.00 (s, 3H)

i.r.: 2850 cm^{-1} ($-OCH_3$ stretching), 1220 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 136 (M^+)

methyl 2,4-di-tert-butylphenyl ether

n.m.r.: δ = 1.31 (s, 9H), 1.40 (s, 9H), 3.80 (s, 3H), 6.75- 7.50 (m, 3H)

i.r.: 2850 cm^{-1} (OCH_3 stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching) 1045 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 220 (M^+)

methyl 2,6-di-tert-butyl-4-methylphenyl ether

n.m.r.: δ = 1.42 (s, 18H), 2.29 (s, 3H), 3.68 (s, 3H), 7.08 (s, 2H)

i.r.: 2850 cm^{-1} (OCH_3 stretching), 1220 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 235 (M^+)

methyl 2,4,6-trimethylphenyl ether

n.m.r.: δ = 2.24 (s, 9H), 3.70 (s, 3H), 6.86 (s, 2H)

i.r.: 2850 cm^{-1} ($-OCH_3$ stretching), 1230 cm^{-1} (Ar-O-C asymmetric stretching) 1020 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 150 (M^+)

ethyl phenyl ether

n.m.r.: δ=1.40 (tr, 3H), 4.08 (qu, 2H), 6.85-7.45 (m, 5H)

i.r.: 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1050 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 122 (M^+)

ethyl 2-nitrophenyl ether

n.m.r.: δ=1.46 (tr, 3H), 4.20 (qu, 2H), 6.9- 7.9 (m, 4H)

i.r.: 1525 cm^{-1}, 1350 cm^{-1} ($-NO_2$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching) 1035 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 167 (M^+)

ethyl 4-nitrophenyl ether m.p., 57-58° (54°C)[42]

n.m.r.: δ=1.46 (tr, 3H), 4.15 (qu, 2H), center at 7.6 (AA'BB', 4H)

i.r.: 1510 cm^{-1}, 1345 cm^{-1} ($-NO_2$ stretching), 1260 cm^{-1} (Ar-O-C asymmetric stretching), 1040 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e=167 (M^+)

ethyl 2-methylphenyl ether

n.m.r.: δ = 1.42 (tr, 3H), 2.25 (s, 3H), 4.05 (qu, 2H), 6.7- 7.3 (m, 4H)

i.r.: 1250 cm^{-1}(Ar-O-C asymmetric stretching), 1050 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 136 (M^+)

ethyl 2,6-dimethylphenyl ether

n.m.r.: δ = 1.42 (tr, 3H), 2.30 (s, 6H), 3.85 (qu, 2H), 7.0 (s, 3H)

i.r.: 1200 cm^{-1}(Ar-O-C asymmetric stretching), 1045 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 150 (M^+)

ethyl 4-fluorophenyl ether

n.m.r.: δ = 1.38 (tr, 3H), 3.95 (qu, 2H), center at 6.90 (m, 4H)

i.r.: 1225 cm^{-1} (Ar-O-C asymmetric stretching), 1050 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 140 (M^+)

benzyl phenyl ether m.p. = 37-38°C

n.m.r.: δ = 5.10 (s, 2H), center at 7.1 (m, 5H), 7.40 (s, 5H)

i.r.: 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1020 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 184 (M^+)

benzyl 2-methylphenyl ether

n.m.r.: δ = 2.30 (s, 3H), 5.10 (s, 2H), centered at 7.10 (m, 4H), 7.41 (s, 5H)

i.r.: 1240 cm^{-1} (Ar-O-C asymmetric stretching), 1025 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 198 (M^+)

benzyl 2-nitrophenyl ether

n.m.r.: δ = 5.25 (s, 2H), 7.45 (s, 5H), centered at 7.50 (m, 4H)

i.r.: 1520 cm^{-1}, 1350 cm^{-} ($-NO_2$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 229 (M^+)

benzyl 4-nitrophenyl ether m.p. = 105-106°C (106°C)[42]

n.m.r.: δ = 5.20 (s, 2H), 7.45 (s, 5H), centered at 7.65 (AA'BB', 4H)

i.r.: 1520 cm^{-1}, 1350 cm^{-1} ($-NO_2$ stretching), 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1005 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 229 (M^+)

benzyl 4-fluorophenyl ether m.p. = 47-48°C

n.m.r.: δ = 5.10 (s, 2H), centered at 7.0 (A_2B_2, 4H), 7.41 (s, 5H)

i.r.: 1210 cm^{-1}(Ar-O-C asymmetric stretching), 1025 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 202 (M^+)

benzyl 2,6-dimethylphenyl ether

n.m.r.: δ = 2.32 (s, 6H), 4.82 (s, 2H), 7.02 (s, 3H), 7.05 (s, 5H)

i.r.: 1200 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 212 (M^+)

benzyl 2,4-di-tert-butylphenyl ether m.p. 88-89°C

n.m.r.: δ = 1.34 (s, 9H), 1.46 (s, 9H), 5.20 (s, 2H), centered at 7.30 (m, 8H)

i.r.: 1200 cm^{-1} (Ar-O-C asymmetric stretching), 1010 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 296 (M^+)

benzyl 2,4,6-trimethylphenyl ether

n.m.r.: δ = 2.24 (s, 9H), 4.80 (s, 2H), 6.88 (s, 2H), centered at 7.45 (m, 7H)

i.r.: 1210 cm^{-1} (Ar-O-C asymmetric stretching), 1020 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 226 (M^+)

benzyl 2-naphthyl ether m.p. = 100-101° (101°C)[42]

n.m.r.: δ = 5.2 (s, 2H), centered at 7.5 (m, 12H)

i.r.: 1250 cm^{-1} (Ar-O-C asymmetric stretching), 1025 cm^{-1} (Ar-O-C symmetric stretching)

m.s.: m/e = 234 (M^+)

di-tert-butyl-p-benzoquinone m.p. = 64-66°C (66°C)[90]

n.m.r.: δ = 1.38 (s, 18H), 6.56 (s, 2H)

i.r.: 1640 cm^{-1} (C=O stretching), 1605 cm^{-1} (C=C stretching)

m.s.: m/e = 220 (M^+)

3,3',5,5'-tetra-tert-butyl-diphenoquinone m.p. = 247-249°C (246°C)[90]

n.m.r.: δ = 1.36 (s, 36H), 7.75 (s, 21H)

i.r.: 1650 cm^{-1} (C=O stretching), 1600 cm^{-1} (C=C stretching)

m.s.: m/e = 401 (M^+)

Chapter VI

Preparation of benzyl alkyl ethers

It has been mentioned previously that the Williamson procedure is by far the most common method used to prepare ethers. The conventional procedure involves the use of sodium metal, a method which can be quite dangerous, tedious and expensive, and therefore a lot of work has been done to try to modify the procedure and to find new reagents to replace the sodium metal.[76,77] Zimmerinan and Darthe reported sodium metal can be replaced by sodium hydroxide in the generation of alkoxide ions, that react with alkyl halides to give ether.[96] Later, Smith, Vanterpool and Kulak attempted the same reaction in dimethylsulfoxide and found that the results are better than those of the conventional procedure.[97] Recently, several new reagents have been used in the synthesis of dialkyl ether. Alcohols can be methylated by dimethyl sulphate in the presence of phase transfer catalyst, or sodium methyl sulphinyl carbanion, or sodium hydride.[98,99,100] The reaction of thallium(I) salts of alcohols with primary alkyl halides also gives ethers.[101] Yamashita and Takagami found that bis(acetylacetonate)nickel is an efficient catalyst for the synthesis of ethers from alcohols and alkyl halides.[102]

In the reaction of n-hexyl bromide with potassium fluoride in several glycols, Kiteno and Fukui found that not only n-hexyl fluoride, but also monoalkyl ethers of the glycols are obtained.[103] When potassium chloride was used instead of potassium fluoride, only n-hexyl chloride and n-hexyl bromide were obtained. No monoalkyl ethers of the glycols were obtained. They also found that only ethylene oxide is obtained in the reaction of excess potassium fluoride with 2-chloroethanol.[104] Only 2-bromoethanol was isolated when

potassium bromide was used. In a study of halide anions as proton acceptors in hydrogen bonding, Allerhand and Schleyer found that fluoride ion forms a hydrogen bond with methanol.[31] From this information, it can be postulated that the formation of monoalkyl ethers of the glycols could be due to the formation of hydrogen bonds between fluoride and the glycols, which may be capable of generating the organic nucleophile. Thus several alcohols were used in the reactions with benzyl chloride or benzyl bromide in the presence of fluoride to examine whether the product is either benzyl alkyl ether or benzyl fluoride. Benzyl halides are chosen because of the high boiling point of benzyl alkyl ethers which makes the ethers easier to separate.

Experimental

Materials

The alcohols were purified by distillation followed by drying over 5 Å molecular sieves. Potassium fluoride and cesium fluoride were commercial samples dried at 100°C *in vacuo* for several hours. Other reagents were generally commercial samples used as obtained.

Reactions

The technique used in each case was the same. Details of a representative preparation are given below:

The reaction of methanol and benzyl bromide in the presence of cesium fluoride

Cesium fluoride (0.02 mol) was dissolved in methanol (10 g). To this solution, benzyl bromide (0.01 mole) was added, the whole was stirred at room temperature. The reaction was stopped after 24 hours. The reaction mixture was extracted into diethyl ether, washed with water, dried (magnesium sulphate) and evaporated to remove the ether. A colorless liquid was isolated and then qualitatively analysed by gas chromatography/mass spectrometry. After the identification of the components in the mixture, the mixtures were analyzed quantitatively, by gas chromatography on an SE-30 column (92% benzyl methyl ether, 6% benzyl fluoride and 2% benzyl bromide).

Results and discussion

As with the carboxylic acid/fluoride system discussed previously, when cesium fluoride was dissolved in methanol, the solution became warm. It was observed that the cesium fluoride was more soluble in methanol than in the other alcohols, but no attempt was made to determine the solubilities of cesium fluoride in the alcohols as part of this work. When benzyl chloride and excess methanol were refluxed together in the presence of potassium fluoride for 24 hours, a colorless liquid was obtained after separation. From gas chromatography/mass spectrometry data, the mixture was shown to consist of three components having parent ions at m/e = 110, 122 and 126, respectively. They could be benzyl fluoride (m/e = 110), methyl benzyl ether (m/e = 122) and benzyl chloride (m/e = 126). The formation of benzyl fluoride and methyl benzyl ether was confirmed by a proton magnetic resonance spectrum. A doublet, J = 48 cps, centered at δ = 5.4 ppm was found; this was the resonance for the benzyl protons of benzyl fluoride. A singlet at δ = 3.42 was found, this was due to the methyl protons of benzyl methyl ether. When benzyl bromide was used, the reaction could be carried out at room temperature and gave the same results. A series of alcohols was reacted with benzyl bromide to determine the limitation, if any, of the type of alcohols which could be used in the synthesis. All the products, except the ethers of 1-propanol and 2-propanol, were analyzed by gas chromatography. The boiling points of these two ethers were very close to benzyl bromide and they could not be separated and analyzed by gas chromatography on the SE30 column routinely used. They were, however, analyzed by proton magnetic

resonance. Therefore, the accuracy of the results may be slightly different from those derived by gas chromatography analysis. The results are summarized in Table V.

From Table V, we see that methanol gave the highest yield of ether. Ethanol, 1-propanol, 2-propanol and tert-butyl alcohol gave relatively poor yields of ethers. Attempts to methylate cyclohexanol failed. Two factors may govern the formation of these ethers. Firstly, the substituted methyl groups at the carbon bearing the hydroxyl group could cause some steric hindrance and, thus, retard the reaction. Secondly, the α-substituents affected the hydrogen bonding ability of the alcohol similarly to the effect observed in the carboxylic acid system. This time, the α-substituents were closer to the hydrogen bonding site, and therefore, the effect should larger and more direct.

From the above results, several conclusions could be reached. Methanol formed the strongest hydrogen bond to fluoride in the aliphatic alcohols series. Compared with the carboxylic acids and the phenols, these alcohols only formed a relatively weak hydrogen bond with the fluoride ion. Since the hydrogen bond was rather weak, it did not enhance the reactivity of the alcohol molecule as much as occurs in the carboxylic acid and phenol series, where the fluoride ion was still an effective nucleophile enabling halide ion exchange to occur. From the synthetic point of view, the aliphatic alcohol-fluoride system is not a particularly good reaction system.

Table V. Products obtained from the reaction of benzyl bromide with alcohols[a]

	% formation of ether	% formation of fluoride	% of unconverted benzyl bromide
Methanol	92	6	2
Ethanol	69	13.0	9.0
1-Propanol[b]	21	19.0	60
2-Propanol[b]	24	20.0	56
tert-Butyl alcohol	41	43	7.0
1-Butanol[c]	70	14	9.0

[a] The reactions were carried out at room temperature for 24 hours. Product mixtures were analyzed by G.C.

[b] Product mixtures were analyzed by proton magnetic resonance spectroscopy.

[c] Reaction time was 48 hours.

Chapter VII

C- and O-alkylation, sulphenylation and Michael additions aided by polymer immobilized fluoride ion

Since Merrifield used insoluble polymer supports to facilitate the synthesis of polypeptides, this new synthetic method has been the subject of much interest in the past fifteen years.[105] A number of useful synthetic applications of the polymer bound supports in repetitive sequential-type organic synthesis of polynucleotides and polysaccharides have been reported.[106,107] It is only recently that the insoluble polymers have been used in general organic synthesis. They can be used for a wide variety of purposes to solve specific synthetic problems. Recently, Cainelli reported that alkyl fluorides can be obtained from alkyl halides or alkyl methane sulphonates by using a F^-... resin.[108] As we have shown previously, fluoride ion can assist organic reactions via strong hydrogen bonding. Attempts were thus made to use this F^- form of strongly basic anion exchange resins to carry out reactions analogous to the "strong hydrogen bond assisted reactions" described in earlier chapters of this thesis.

Experimental

Materials

All the chemical used were commercially available and used without purification. Dimethylformamide and tetrahydrofuran were dried over 5Å molecular sieve for several days before use. Four types of resins, Dowex 1X2, Dowex MSA-1, Amberlyst A26 and A27, were used, these all being commercially available.

Preparation of the resins in F^- form

All the resins were prepared in the same way. Details of a representative preparation are given below.

Dowex MSA1, F^- form

Dowex MSA1, Cl^--form is converted to the OH^- form by washing with 4% sodium hydroxide solution and then rinsing thoroughly with distilled water until neutrality. There were two ways to convert the resin into F^- form. First, the OH^- form of the resin was stirred overnight with an excess of 1N aqueous hydrogen fluoride, washed with acetone and ether, and dried at 50° for 4 hours under vacuum. The second one, the OH^- form resins were washed with 4% potassium fluoride solution until the eluent was not basic, then washed with acetone and ether, and dried.

The capacity of OH^--form of MSA is determined by adding the resin (1 g) to 20 ml 1N hydrochloric acid, allowing the mixture to reach equilibrium overnight, and then titrating the excess hydrochloric acid with standard base. The capacity was 1.2 mequiv/g for MSA1 and Dowex 1X2, 0.97 mequiv/ml for Amberlyst A26.

Reactions

The technique used in each case was the same. An example is given below.

The sulphenylation of β-dicarbonyls

To the dry resin (10 g, 0.012 mole F^-), acetylacetone (1g, 0.01 mole) was added. N,N-Dimethylformamide (30 ml) was added along with benzenethiol (1.1 g, 0.01 mole). The mixture was stirred at 60°C for 24 hours. After separation and washing the resin with diethyl ether, the ethereal solution was dried (magnesium sulphate) and evaporated. The product was analyzed by proton magnetic resonance.

Results and Discussion

In this preliminary study, the first reaction in which we attempted to use polymer bound supports as a fluoride ion source, was the sulphenylation of β-dicarbonyls. Selection of this reaction was due to the fact that the proton magnetic resonance spectra of the expected product, α-thio-β-dicarbonyl, is quite simple and is easy to recognize. 3-Benzenethio-pentane-2,4-dione is present only in the enol form, and this ensured that α-thio-β-dicarbonyl and free β-dicarbonyl can be distinguished by means of proton magnetic resonance.[29] Two types of resins, Dowex MSA1 and Dowex 1X-2, were used in the reaction. The low crosslinkage analytical resin, Dowex 1X-2 gave poor results. Dowex MSA-1 macroporous resin gave about 75% reaction. The next reaction attempted was the methylation of β-dicarbonyl compounds. Since the starting material and the product were present as enol-keto tautomers, the proton magnetic resonance spectra of the final product could be complicated. Fortunately, the tautomeric equilibria of β-dicarbonyls have been investigated by Burdett and Rogers using nuclear magnetic resonance spectroscopy.[109] Proton chemical shift measurements have been carried out on a series of acyclic compounds, and equilibrium constants have been determined.[109] Therefore, the percentage of the reaction can be calculated based on this information. It was found that Amberlyst A26 and A27 macroreticular resins give better results than Dowex MSA-1 macroporous resin. The Amberlyst resins were specifically designed for use in non-aqueous solvents. At room temperature in tetrahydrofuran, the MAS-1 showed no reaction. In a Michael addition with Dowex MSA-1, the reaction was 80% completed. In O-alkylation of phenols,

only 50% reaction occurred. No reaction was observed when no resin was used or if the resin in chloride form was used under the same conditions. This indicated that fluoride is a necessary ingredient. Table VI summarizes the resin reactions.

In a review of the use of insoluble polymer supports in organic chemical synthesis, Leznoff pointed out that the steric effect of the polymer backbone can be used to advantage for some synthetic purposes, more often the insoluble polymer imparts a certain steric hindrance to the reaction, which varies with the substrate and reaction attempted.[110] This may explain how it is that C-alkylation of β-dicarbonyl compound gives better results than O-alkylation of phenol. The solvents, the type of resins, and temperature were all quite important in the reaction. They vary from reaction to reaction. No attempt has been made in this work to find out the optimum reaction conditions to improve yields, but a more detailed study of these resin systems by S. R. Cater is in progress in this laboratory.

Table VI. Results of C- and O-alkylation, sulphenylation and Michael additions

Reactants	Products	Time (h)	Temp (°C)	Solvent	Yield (%)	Resin (F^- form)
C-alkylation						
$CH_3C(=O)CH_2C(=O)CH_3 + CH_3I$	$CH_3C(=O)CH(CH_3)C(=O)CH_3$	48	60	DMF	70	Dowex MSA-1
" "	"	24	20	THF	0	"
" "	"	24	20	THF	60	Amberlyst A26
" "	"	24	20	THF	70	Amberlyst A27
O-alkylation						
$C_6H_5OH + CH_3I$	$C_6H_5OCH_3$	24	60	DMF	50	Dowex MSA-1
$p\text{-}NO_2C_6H_4OH + CH_3I$	$p\text{-}NO_2C_6H_4OCH_3$	24	60	DMF	50	Dowex MSA-1
Sulphenylation						
$CH_3C(=O)CH_2C(=O)CH_3 + C_6H_5SH$ + air	$CH_3C(=O)CH(SC_6H_5)C(=O)CH_3$	24	60	DMF	75	Dowex MSA-1
" $+ C_6H_5SSC_6H_5$	"	24	60	DMF	75	Dowex MSA-1
Michael Addition						
$CH_3C(=O)CH=CH_2 + C_6H_5SH$	$CH_3C(=O)CH_2CH_2SC_6H_5$	24	20	THF	80	Dowex MSA-1

Chapter VIII

General Discussion

From the results of this research, it can be seen that the fluoride-carboxylic acids, fluoride-phenols and fluoride-2-nitropropane are useful reaction systems. The fluoride-alcohol systems, with the notable exception of cesium fluoride-methanol, gave less useful results. This may be due to the fact that the fluoride-alcohol hydrogen bond has less effect on the nucleophilicity of the organic molecule and the fluoride ion remains an effective nucleophile enabling fluorination to occur.

The mechanism of the hydrogen bond assisted reactions

Most of the reactions described in the previous chapters can be carried out in the presence of bases. But their mechanisms are slightly different from those of the hydrogen bond-assisted reactions. In the former case, the base probably forms a hydrogen bonded complex with the reactant molecule, but it is very short-lived, so that the active species in the reaction is the organic anion. In the hydrogen bond-assisted reaction, the fluoride forms a highly reactive anionic complex by hydrogen bonding to the most acidic

$$R'YH + Base \longrightarrow (R'Y...H...Base) \longrightarrow R'Y^- + Base\text{-}H^+$$

$$R'Y^- + RX \longrightarrow R'YR + X^-$$

$R'Y = RCO_2$, PhO and RO

proton of the reactant molecule. This anionic complex is quite stable and no proton transfer leading to the anion of the organic molecule occurs. This

complex is capable of carrying out a nucleophilic substitution reaction to give the product. Thus, while all bases indubitably operate by the initial

$$R'YH + F^- \longrightarrow (R'Y...H...F)^-$$

$$(R'Y...H...F)^- + RX \longrightarrow R'YR + HFX$$

$R'Y = RCO_2$, PhO and RO

formation of a hydrogen bonded complex to the reactant protic species, it is proposed that the life time of these complexes is dependent on the base. The life time of a hydride ion complex is presumably very short, so that the effective nucleophilic species is the organic anion, however, the stability of the fluoride-organic molecule anionic complex by comparison, may well result in the hydrogen bonded complex playing a major role in the subsequent reaction.

Reaction conditions

The choice of both fluoride and solvent is critical in determining the rate, and perhaps the course of the reaction. Several fluorides, such as alkali metal fluorides, tetraethylammonium fluoride and immobile polymer fluoride, were used in this research. Alkali metal fluorides, especially potassium fluoride, were most commonly used in the previous account of hydrogen bond assisted reactions. They are slightly soluble in organic solvents and it is believed that the reaction could be occurring, in part, on the surface of suspended fluoride. Tetraethylammonium fluoride is more soluble in organic solvents and it seems that here the reactions occur in solution. The use of immobile polymer fluoride in organic synthesis is a very recent aspect of this work which is still under investigation.

The source of fluoride sometimes changes the rate of reaction. For example, in the reaction of phenol and alkyl halides and the reaction of 2-nitropropane and benzyl halide, when potassium fluoride was used, the reaction took a longer time and higher temperature to complete; in the latter case, no reaction occurred. When tetraethylammonium fluoride was used, the reactions were complete in shorter time and at lower temperatures. Clark and Miller similarly observed that cesium fluoride was more effective than potassium fluoride, and tetraalkylammonium fluorides were more efficient than alkali metal fluorides. They explained that an ion pair of the (cation)-(F...electron acceptor anion) may be required to form preceding the reaction.[111] For some larger organic molecules, such as phenol and 2-nitropropane, larger cations are needed. Thus it is wise to consider the source of fluoride ion before beginning any hydrogen bond assisted organic reaction.

Aprotic solvents such as N,N-dimethylformamide, tetrahydrofuran and dimethyl sulphoxide were used as solvents for most of the reactions described in this research. If protic solvents, such as alcohols, were employed, they could reduce the rates of reaction by competition with the reactant electron acceptor for the fluoride anion. With stronger electron acceptors, such as carboxylic acids and phenols, the use of a protic solvent will have little influence on the very strong fluoride-acid hydrogen bond; however, with weaker electron acceptors, such as amines, benzene and thiols, the hydrogen bond will be seriously affected and may alter the course of the reactions. The choice of solvent is thus important in hydrogen bond-assisted reactions.

It is clear from this research and related work that hydrogen bonding may well continue to play an important role in synthetic chemistry.

Instrumentation

Nuclear magnetic resonance spectra were recorded on a Varian A60 spectrometer operating at 60 MHz using deuterochloroform as solvent, and tetramethylsilane as internal standard.

Infrared spectra were recorded on a Perkin-Elmer Model 237B and Model 735 Grating Infrared spectrophotometer using the standard liquid film and pellet form (potassium bromide) technique.

Mass spectra were recorded on a MS30 double beam mass spectrometer. Gas-liquid chromatography/mass spectrometry analyses were carried out using a MS30 double beam mass spectrometer with a 3% SE30 Chrom W(80-200 mesh) column.

Analytical gas-liquid chromatograms were obtained on a Varian Model A90-P3 Aerograph with a 20% SE30 on 60/80 AW DMSC column. Helium was the carrier gas. Quantitative work was carried out using benzyl bromide as internal standard; product ratios were determined with a Model 224 disc chart integrator.

Melting points were determined on a Kofler hot stage microscope apparatus and are uncorrected.

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